10/511,089

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2680	514/249 OR 544/354	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/05 14:17
L2	3	L1 AND (ZONAMPANEL OR 2, 3-DIOXO-3,4-DIHYDRO OR ".ALPHA. -CRYSTAL" OR (FREE ADJ FORM ADJ ANHYDRIDE))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/05 14:22
L4	0	ZONAMPANEL	USPAT	OR	OFF	2007/04/05 14:22
L5	0	Zonampanel	USPAT	OR	OFF	2007/04/05 14:22
L6	13	Zonampanel	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/05 14:22
L7	11	L6 NOT L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/05 14:52
L8	1	-6-nitro-2,3-dioxo-	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/05 14:54

— 10/511,089 STN SEARCH TRANSCRIPT —

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  DEC 18  CA/CAplus pre-1967 chemical substance index entries enhanced
                  with preparation role
 NEWS  4  DEC 18  CA/CAplus patent kind codes updated
 NEWS  5  DEC 18  MARPAT to CA/CAplus accession number crossover limit increased
                  to 50,000
 NEWS  6  DEC 18  MEDLINE updated in preparation for 2007 reload
 NEWS  7  DEC 27  CA/CAplus enhanced with more pre-1907 records
 NEWS  8  JAN 08  CHEMLIST enhanced with New Zealand Inventory of Chemicals
 NEWS  9  JAN 16  CA/CAplus Company Name Thesaurus enhanced and reloaded
 NEWS 10  JAN 16  IPC version 2007.01 thesaurus available on STN
 NEWS 11  JAN 16  WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
 NEWS 12  JAN 22  CA/CAplus updated with revised CAS roles
 NEWS 13  JAN 22  CA/CAplus enhanced with patent applications from India
 NEWS 14  JAN 29  PHAR reloaded with new search and display fields
 NEWS 15  JAN 29  CAS Registry Number crossover limit increased to 300,000 in
                  multiple databases
 NEWS 16  FEB 15  PATDPASPC enhanced with Drug Approval numbers
 NEWS 17  FEB 15  RUSSIAPAT enhanced with pre-1994 records
 NEWS 18  FEB 23  KOREAPAT enhanced with IPC 8 features and functionality
 NEWS 19  FEB 26  MEDLINE reloaded with enhancements
 NEWS 20  FEB 26  EMBASE enhanced with Clinical Trial Number field
 NEWS 21  FEB 26  TOXCENTER enhanced with reloaded MEDLINE
 NEWS 22  FEB 26  IFICDB/IFIPAT/IFIUDB reloaded with enhancements
 NEWS 23  FEB 26  CAS Registry Number crossover limit increased from 10,000
                  to 300,000 in multiple databases
 NEWS 24  MAR 15  WPIDS/WPIX enhanced with new FRAGHITSTR display format
 NEWS 25  MAR 16  CASREACT coverage extended
 NEWS 26  MAR 20  MARPAT now updated daily
 NEWS 27  MAR 22  LWPI reloaded
 NEWS 28  MAR 30  RDISCLOSURE reloaded with enhancements
 NEWS 29  MAR 30  INPADOCDB will replace INPADOC on STN
 NEWS 30  APR 02  JICST-EPLUS removed from database clusters and STN

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available

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FILE 'HOME' ENTERED AT 15:19:02 ON 05 APR 2007

=> FILE REG
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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DICTIONARY FILE UPDATES:    4 APR 2007  HIGHEST RN 929190-51-2

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=>
Uploading C:\Program Files\Stnexp\Queries\ZONAMPANEL ANHYDRIDE CRYSTALS.str
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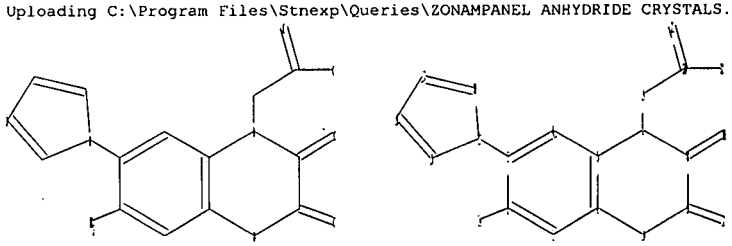

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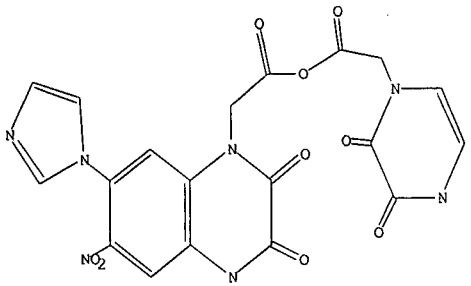
chain nodes :
11  12  14  19  20  21  22
ring nodes :
1  2  3  4  5  6  7  8  9  10  13  15  16  17  18
chain bonds :
2-14  3-13  7-19  8-11  9-12  19-20  20-21  20-22
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-7  6-10  7-8  8-9  9-10  13-15  13-18  15-16  16-17
 17-18
exact/norm bonds :
3-13  5-7  6-10  7-8  7-19  8-9  8-11  9-10  9-12  13-15  13-18  15-16  16-17
20-21  20-22
```

exact bonds :
2-14 17-18 19-20
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6
isolated ring systems :
containing 1 : 13 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:CLASS 13:Atom 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS
20:CLASS 21:CLASS 22:CLASS

L1 STRUCTURE UPLOADED

=> D L1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> S L1
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SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 0 TO 0
PROJECTED ANSWERS: 0 TO 0

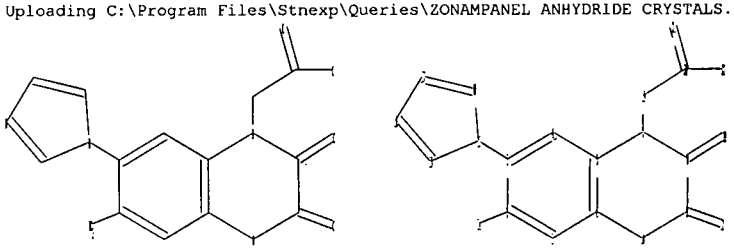
L2 0 SEA SSS SAM L1

=> S L1 SSS FULL
FULL SEARCH INITIATED 15:19:45 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 4 TO ITERATE

100.0% PROCESSED 4 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L3 0 SEA SSS FUL L1

=>
Uploading C:\Program Files\Stnexp\Queries\ZONAMPANEL ANHYDRIDE CRYSTALS.str

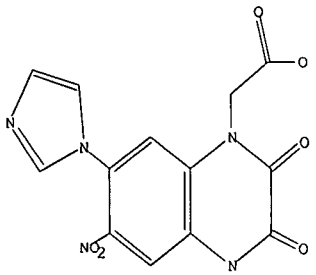


chain nodes :
11 12 14 19 20 21 22
ring nodes :
1 2 3 4 5 6 7 8 9 10 13 15 16 17 18
chain bonds :
2-14 3-13 7-19 8-11 9-12 19-20 20-21 20-22
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 13-15 13-18 15-16 16-17
17-18
exact/norm bonds :
3-13 5-7 6-10 7-8 7-19 8-9 8-11 9-10 9-12 13-15 13-18 15-16 16-17
20-21 20-22
exact bonds :
2-14 17-18 19-20
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6
isolated ring systems :
containing 1 : 13 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:CLASS 13:Atom 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS
20:CLASS 21:CLASS 22:CLASS

L4 STRUCTURE UPLOADED

=> D L4
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

=> S L4 SSS FULL
FULL SEARCH INITIATED 15:20:47 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 172 TO ITERATE

100.0% PROCESSED 172 ITERATIONS 10 ANSWERS
SEARCH TIME: 00.00.01

L5 10 SEA SSS FUL L4

=> FILE CAPLUS

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FULL ESTIMATED COST	344.65	344.86

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FILE LAST UPDATED: 4 Apr 2007 (20070404/ED)

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=> S L5
L6 43 L5

=> S L6 AND ANHYDRIDE
216087 ANHYDRIDE
33238 ANHYDRIDES
226828 ANHYDRIDE
(ANHYDRIDE OR ANHYDRIDES)
L7 0 L6 AND ANHYDRIDE

=> S L6 AND CRYST?
2150797 CRYST?
L8 1 L6 AND CRYST?

=> D IBIB ABS HITSTR

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:837078 CAPLUS
DOCUMENT NUMBER: 139:341724
TITLE: Novel crystals of quinoxalinedione derivative
INVENTOR(S): Yuda, Masamichi; Kohinata, Takeru
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

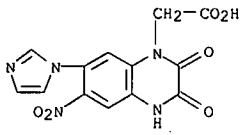
APPLICANTS'

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003087091	A1	20031023	WO 2003-JP4844		20030416
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2482937	A1	20031023	CA 2003-2482937		20030416
AU 2003231361	A1	20031027	AU 2003-231361		20030416
EP 1496057	A1	20050112	EP 2003-725594		20030416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
US 2005130978	A1	20050616	US 2003-511089		20030416
IN 2004DN03150	A	20050401	IN 2004-DN3150		20041013
PRIORITY APPLN. INFO.:			JP 2002-114781	A	20020417
			WO 2003-JP4844	W	20030416

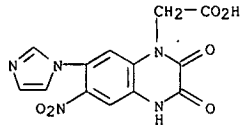
AB Claimed are α crystals of [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid (I); these anhydrous crystals were prepared by drying I monohydrate under reduced pressure for 3 days at 80°C. I is a known AMPA antagonist. The above-mentioned α crystals of I are stable under any humidity conditions. An injectable solution prepared from α crystals of I is disclosed.

IT 210245-80-0
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of α crystals of [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid as AMPA antagonist)

RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



IT 466685-98-3
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(preparation of α crystals of [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid as AMPA antagonist)
RN 466685-98-3 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)



● H_2O

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D HIS

(FILE 'HOME' ENTERED AT 15:19:02 ON 05 APR 2007)

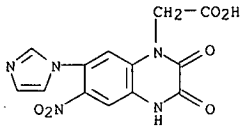
FILE 'REGISTRY' ENTERED AT 15:19:18 ON 05 APR 2007
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 0 S L1 SSS FULL
L4 STRUCTURE UPLOADED
L5 10 S L4 SSS FULL

FILE 'CAPLUS' ENTERED AT 15:20:52 ON 05 APR 2007
L6 43 S L5
L7 0 S L6 AND ANHYDRIDE
L8 1 S L6 AND CRYST?

=> S L6 NOT L8
L9 42 L6 NOT L8

=> D 1-42 IBIB ABS HITSTR

L9 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:399820 CAPLUS
DOCUMENT NUMBER: 145:368979
TITLE: Other Neuroprotective Therapies on Trial in Acute Stroke
AUTHOR(S): Ferro, Jose M.; Davalos, Antoni
CORPORATE SOURCE: Department of Neurosciences and Mental Health, Hospital de Santa Maria, Lisbon, Port.
SOURCE: Cerebrovascular Diseases (Basel, Switzerland) (2006), 21(Suppl. 2), 127-130
CODEN: CDISE7; ISSN: 1015-9770
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. New neuroprotective agents on trial may potentially offer benefit to stroke patients without the associated hemorrhagic risk of thrombolytic therapy. Clin. investigation of these drugs has been designed to obtain the highest probability of success, or concs. on the salvageable ischemic brain and use infarct growth on MRI as a surrogate end-point. Nine substances in 10 trials are currently being tested in three therapeutical strategies in patients with acute ischemic stroke. These strategies focus on: (1) the optimal management of serum glucose with the infusion of glucose, insulin and potassium to induce and maintain euglycemia; (2) the modulation of the inflammatory response with recombinant human interferon-β1a, and (3) interfering with the ischemic cascade using magnesium, albumin, the metal iron chelator DP-b99, the AMPA receptor antagonist zonampanel, the serotonin agonists repinotan and piclozotan, the free radical scavenger cerovive, and the membrane modulator citicoline. Future directions should develop neuroprotective compds. that are safe and well tolerated, are effective in a broad range of patients and can be used with or without rt-PA.
IT 210245-80-0, Zonampanel
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective therapies using AMPA receptor antagonist, zonampanel interferes with ischemic cascade in patient with acute ischemic stroke)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

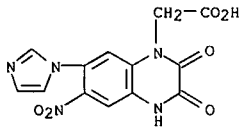
L9 ANSWER 2 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:309639 CAPLUS
DOCUMENT NUMBER: 145:499861
TITLE: 1,026 Experimental treatments in acute stroke
AUTHOR(S): O'Collins, Victoria E.; Macleod, Malcolm R.; Donnan, Geoffrey A.; Horky, Laura L.; van der Worp, Bart H.; Howells, David W.
CORPORATE SOURCE: Neuroscience Lab, Department of Medicine, Austin Health, University of Melbourne, Heidelberg, Australia
SOURCE: Annals of Neurology (2006), 59(3), 467-477
CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: Preclin. evaluation of neuroprotectants fostered high expectations of clin. efficacy. When not matched, the question arises whether expts. are poor indicators of clin. outcome or whether the best drugs were not taken forward to clin. trial. Therefore, we endeavored to contrast exptl. efficacy and scope of testing of drugs used clin. and

those tested only exptl. Methods: We identified neuroprotectants and reports of exptl. efficacy via a systematic search. Controlled in vivo and in vitro expts. using functional or histol. end points were selected for anal. Relationships between outcome, drug mechanism, scope of testing, and clin. trial status were assessed statistically. Results: There was no evidence that drugs used clin. (114 drugs) were more effective exptl. than those tested only in animal models (912 drugs), for example, improvement in focal models averaged 31.3±16.7% vs. 24.4±32.9%, $p > 0.05$, resp. Scope of testing using Stroke Therapy Academic Industry Roundtable (STAIR) criteria was highly variable, and no relationship was found between mechanism and efficacy. Interpretation: The results question whether the most efficacious drugs are being selected for stroke clin. trials. This may partially explain the slow progress in developing treatments. Greater rigor in the conduct, reporting, and anal. of animal data will improve the transition of scientific advances from bench to bedside.

IT 210245-80-0, YM872
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(STAIR criteria indicated no evidence that neuroprotective drugs including radix salviae miltiorrhizae used in acute stroke patient were more effective exptl. than those tested in hamster model of focal ischemia)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:169374 CAPLUS

DOCUMENT NUMBER: 145:180705

TITLE: The Effects of an AMPA Receptor Antagonist on the Neurotoxicity of Tetracaine Intrathecally Administered in Rabbits

AUTHOR(S): Koizumi, Yumika; Matsumoto, Mishiya; Yamashita, Atsuo; Tsuruta, Shunsuke; Ohtake, Takanao; Sakabe, Takefumi

CORPORATE SOURCE: Department of Anesthesiology-Resuscitology, Yamaguchi University School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi, 755-8505, Japan

SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States) (2006), 102(3), 930-936
CODEN: AACRAT; ISSN: 0003-2999

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

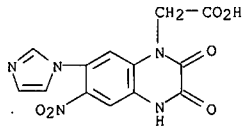
LANGUAGE: English

AB We have reported that large concns. of intrathecal local anesthetics increase glutamate concns. in the cerebrospinal fluid (CSF) and cause neuronal injury in rabbits. In the current study we determined whether an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist, YM872, administered intrathecally, reduces neuronal injury caused by tetracaine. We first examined the effects of intrathecal YM872 10, 30, 100, or 300 μg in rabbits (n = 3 in each). YM872 produced reversible motor and sensory block in a dose-dependent manner. Then, we evaluated modulatory effects of YM872 (300 μg) on tetracaine-induced glutamate release and neuronal injury. Pretreatment of YM872 did not attenuate 1% or 2% tetracaine-induced increases in cerebrospinal fluid glutamate concns. (n = 3 in each). For evaluation of neuronal injury, rabbits were assigned to 4 groups (n = 6 in each) and intrathecally received 1% tetracaine and saline (1%T), 1% tetracaine and YM872 (1%TY), 2% tetracaine and saline (2%T), or 2% tetracaine and YM872 (2%TY). The volume of saline, YM872, and tetracaine was 0.3 mL. Saline or YM872 was administered 30 min before tetracaine administration. Neurol. and histopathol. assessments were performed 1 wk after the administration. Two and 1 animals resp., showed motor and sensory dysfunction in 1%T, whereas 5 animals showed both motor and sensory dysfunction in 2%T. YM872 improved 2% tetracaine-induced motor dysfunction and neuronal damage (chromatolytic neurons, identified by round-shaped cytoplasm with loss of Nissl substance from the central part of the cell and eccentric nuclei). In 2%TY, 3 animals showed normal motor function and 3 showed mild dysfunction (ability to hop, but not normally), whereas 4 animals showed moderate dysfunction (inability to hop) in 2%T ($P = 0.042$). Only 2 animals showed one chromatolytic neuron in 2%TY, whereas 5 animals showed 4-16 chromatolytic neurons in 2%T ($P = 0.020$). These results suggest that AMPA receptor activation is involved, at least in part, in the tetracaine-induced neurotoxicity in the spinal cord.

IT 210245-80-0, YM872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intrathecal administration of AMPA receptor antagonist YM872 reduced tetracaine-induced neurol. and histopathol. damage by improving motor dysfunction and reducing number of chromatolytic neurons in spinal cord of rabbit model)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:133089 CAPLUS

DOCUMENT NUMBER: 144:247072

TITLE: Effect of YM872, a selective and highly water-soluble AMPA receptor antagonist, in the rat kindling and rekindling model of epilepsy

AUTHOR(S): Hara, Hiroshi; Yamada, Norihito; Kodama, Masazumi; Matsumoto, Yosuke; Wake, Yosuke; Kuroda, Shigetoshi

CORPORATE SOURCE: Department of Neuropsychiatry, Okayama University Graduate School of Medicine and Dentistry, Okayama City, Okayama, 700-8558, Japan

SOURCE: European Journal of Pharmacology (2006), 531(1-3), 59-65
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

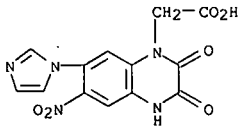
AB We examined antiepileptogenic and anticonvulsant effects of [2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]-

acetic acid monohydrate (YM872), a potent and highly water-soluble alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptor antagonist, in the rat amygdala kindling model of epilepsy. Administration of YM872 significantly suppressed fully kindled seizures. Daily pretreatment with YM872 markedly retarded development of kindling during drug sessions. We also used the rekindling method to investigate the antiepileptogenic effect of YM872 in an attempt to differentiate between true and false effects in the conventional method of daily administration. The results using the rekindling method suggested that the effect of YM872 was truly antiepileptogenic, indicating its possible clin. usefulness as an antiepileptogenic drug. We also affirmed the importance of AMPA receptors in the seizure expression mechanism and development of kindling-induced epileptogenesis.

IT 210245-80-0, YM872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of highly water-soluble AMPA receptor antagonist YM872 in epilepsy)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:1301881 CAPLUS

DOCUMENT NUMBER: 144:120917

TITLE: Design and synthesis of novel 7-heterocycle-6-trifluoromethyl-3-oxoquinoxaline-2-carboxylic acids bearing a substituted phenyl group as superior AMPA receptor antagonists with good physicochemical properties

AUTHOR(S): Takano, Yasuo; Shiga, Futoshi; Asano, Jun; Hori, Wataru; Fukuchi, Kazunori; Anraku, Tsuyoshi; Uno, Takashi

CORPORATE SOURCE: Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd., 2399-1, Nogi, Nogi-machi, Simotsuga-gun, Tochigi, 329-0114, Japan

SOURCE: Bioorganic & Medicinal Chemistry (2006), 14(3), 776-792
CODEN: BMECEP; ISSN: 0968-0896

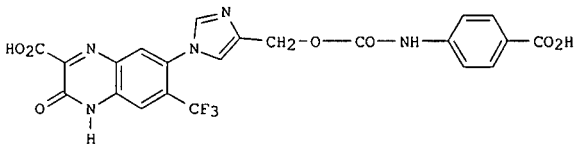
PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 144:120917

GI



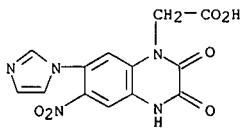
I

AB We describe the design, synthesis, and physicochem. and biol. properties of a novel series of 7-heterocycle-6-trifluoromethyl-3-oxoquinoxaline-2-carboxylic acids bearing a substituted Ph group joined through a urethane or urea linkage to the heterocycle at the 7 position. Introduction of the trifluoromethyl group at the 6 position conferred good biol. activity, including neuroprotective effects, as well as good physicochem. properties. In terms of α-amino-3-hydroxy-5-methylisoxazole propionate receptor (AMPA-R) affinity, a urea linkage was equivalent to a urethane linkage and a pyrrole ring at the 7 position reduced affinity in comparison with an imidazole ring. Among this series, compound I (KRP-199), which has a 4-carboxyphenyl group joined through a urethane linkage to a 7-imidazolyl heterocycle, was found to possess high potency and selectivity for the AMPA-R in vitro and to exhibit good neuroprotective effects in vivo. Furthermore, the compound showed good physicochem. properties, including stability to light and good solubility in aqueous solns.

IT 210245-80-0, Ym 872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AMPA receptor antagonist and neuroprotectant heterocyclic trifluoromethyloxoquinoxalinecarboxylates)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:518632 CAPLUS

DOCUMENT NUMBER: 143:259428

TITLE: Identification of metabolites of [14C]zonampanel, an α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist, following intravenous infusion in healthy volunteers

AUTHOR(S): Minematsu, T.; Sohda, K.-Y.; Hashimoto, T.; Imai, H.; Usui, T.; Kamimura, H.

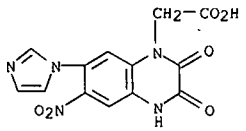
CORPORATE SOURCE: Drug Metabolism Laboratories, Yamanouchi Pharmaceutical, Co. Ltd, Tokyo, Japan

SOURCE: Xenobiotica (2005), 35(4), 359-371

CODEN: XENOBH; ISSN: 0049-8254
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study determined the pharmacokinetics, metabolism and excretion of an α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist zonampanel monohydrate (YM872) after i.v. infusion of [14C]YM872 at 1 mg kg-1 h-1 for 2h to four healthy male volunteers. Mean pharmacokinetic parameters of unchanged YM872 were 0.78h for terminal half-life, 25.91 h-1 for total clearance, 22.91 h-1 for renal clearance, and 15.61 for volume of distribution at steady-state. Urinary excretion of radioactivity accounted for 94.9% of the dose, and fecal excretion for only 0.5% of the dose. Measurement of YM872 concns. by a high-performance liquid chromatog. (HPLC)-UV method and radiometric HPLC metabolite profiling revealed that almost all of [14C]YM872 was excreted unchanged in the urine and that unchanged [14C]YM872 was the major circulating [14C] component in the plasma. Two minor metabolites, H1 and H2, detected in the urine and identified as the same chemical structures as those of the rat urinary metabolites, have a hydroxyamino group and an amino group, resp., which were probably formed by reduction of the nitro group of YM872. These results show that virtually all of the administered YM872 remains unchanged, with urinary excretion representing the major elimination pathway. The high renal clearance implies tubular secretion of this drug.

IT 210245-80-0, Zonampanel
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabolites of zonampanel following i.v. infusion in healthy volunteers)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:471966 CAPLUS
DOCUMENT NUMBER: 143:13349
TITLE: Combinations comprising AMPA receptor antagonists for the treatment of tinnitus
INVENTOR(S): Lingenhoehl, Kurt; Ofner, Silvio; Karolchyk, Mary Ann
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

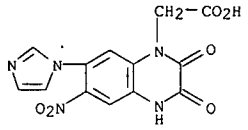
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005049042	A1	20050602	WO 2004-EP12263	20041029

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-25390 A 20031030
OTHER SOURCE(S): MARPAT 143:13349

AB The present invention relates to combinations suitable for the treatment of neurol. disorders, in particular tinnitus. The combinations comprise at least one AMPA receptor antagonist and at least one compound selected from the group consisting of ant-anxiety drugs, antidepressants, antihistamines, anticonvulsants, vasodilators, zinc salts and anesthetics.

IT 210245-80-0, Zonampanel
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations comprising AMPA receptor antagonists for the treatment of tinnitus)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:76247 CAPLUS
DOCUMENT NUMBER: 142:148812
TITLE: Compositions of a cyclooxygenase-2 selective inhibitor and a non-NMDA glutamate modulator for the treatment of central nervous system damage
INVENTOR(S): Stephenson, Diane T.; Taylor, Duncan P.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 150 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007106	A2	20050127	WO 2004-US22189	20040708
WO 2005007106	A3	20060608		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,

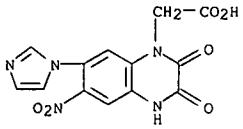
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005101597 A1 20050512 US 2004-887035 20040708
PRIORITY APPLN. INFO.: US 2003-486654P P 20030710
OTHER SOURCE(S): MARPAT 142:148812

AB The invention provides compns. and methods for the treatment of central nervous system damage in a subject. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic condition or a central nervous system traumatic injury comprising the administration to a subject of a non-NMDA glutamate modulator in combination with a cyclooxygenase-2 selective inhibitor.

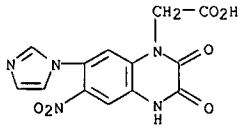
IT 466685-98-3 466685-98-3D, prodrug derivs. and esters
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 selective inhibitor combination with non-NMDA glutamate modulator for treatment of central nervous system damage)

RN 466685-98-3 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)



● H_2O

RN 466685-98-3 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)



● H_2O

L9 ANSWER 9 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:29217 CAPLUS
DOCUMENT NUMBER: 142:141234
TITLE: Delivering polymerized therapeutic agent compositions
INVENTOR(S): Waugh, Jacob; Razavi, Mahmood; Rhee, Ceron; Bryant, Clifford
PATENT ASSIGNEE(S): Polycord, Inc., USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

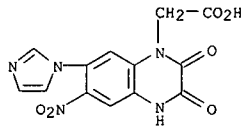
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002597	A1	20050113	WO 2004-US21453	20040702
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005074425	A1	20050407	US 2004-884226	20040702
PRIORITY APPLN. INFO.:			US 2003-485076P	P 20030702
			US 2004-884226	A 20040702

AB A method for delivering polymerized therapeutic agents and their compns. are disclosed. The various polymers take advantage of the functional domains found in a variety of therapeutic agents. The polymerized therapeutic agent compns. are prepared by covalently linking the agent to a biocompatible backbone either directly or through backbone conjugates/monomers. The polymerized therapeutic agent compns. of the invention have highly desirable properties, which make them particularly well suited for use in biol. and biomedical applications. An example is polyaspartate with rofecoxib-OH derivative ester side chains.

IT 210245-80-0, YM 872
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(delivering polymerized therapeutic agent compns.)

RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1374 CAPLUS
DOCUMENT NUMBER: 142:211370
TITLE: Application of LC-NMR for characterization of rat urinary metabolites of zonampanel monohydrate (YM872)
AUTHOR(S): Sohda, Kin-ya; Minematsu, Tsuyoshi; Hashimoto, Tadashi; Suzumura, Ken-ichi; Funatsu, Masashi; Suzuki, Katsuhiro; Imai, Harumitsu; Usui, Takashi; Kamimura, Hidetaka
CORPORATE SOURCE: Drug Metabolism Laboratories, Drug Development Division, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, 174-8511, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (2004), 52(11), 1322-1325
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal

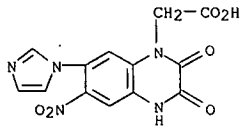
LANGUAGE: English

AB Zonampanel monohydrate (YM872) has a potent and selective antagonistic effect on the glutamate receptor subtype, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor. Metabolic fingerprinting in rat urine after a single i.v. administration of 14C-labeled YM872 (14C-YM872) revealed the presence of two metabolites, R1 and R2. The two metabolites were semi-purified by preparative HPLC from rat urine after a single i.v. administration of non-labeled YM872, and their structures were elucidated by various instrumental analyses involving LC-NMR. The results showed that R1 and R2 have a hydroxyamino group and an amino group at the C-7 position of the quinoxalinedione skeleton, resp. Therefore, the proposed metabolic pathway of YM872 in rats involves the reduction of the nitro group to a hydroxyamino group and then subsequent reduction to an amino group.

IT 466685-98-3, Zonampanel monohydrate
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)
(application of LC-NMR for characterization of rat urinary metabolites of zonampanel monohydrate)

RN 466685-98-3 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)



● H_2O

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:829671 CAPLUS

DOCUMENT NUMBER: 141:307003

TITLE: Characterization of the renal tubular transport of zonampanel, a novel α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, by human organic anion transporters

AUTHOR(S): Hashimoto, Tadashi; Narikawa, Shinichi; Huang, Xiu-Lin; Minematsu, Tsuyoshi; Usui, Takashi; Kamimura, Hidetaka; Endou, Hitoshi

CORPORATE SOURCE: Drug Metabolism Laboratories, Drug Development Division, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan

SOURCE: Drug Metabolism and Disposition (2004), 32(10), 1096-1102
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

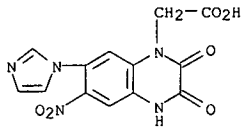
LANGUAGE: English

AB Zonampanel monohydrate (YM872; [2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]acetic acid monohydrate) is a novel AMPA receptor antagonist. The major elimination route for zonampanel has been reported to be by urine via the kidneys. The purpose of this study is to elucidate the mol. mechanism of the renal excretion of zonampanel using cells stably expressing human organic anion transporters (hOAT) 1, hOAT2, hOAT3, and hOAT4, as well as human organic cation transporters (hOCT) 1 and hOCT2. Another AMPA receptor antagonist, YM90K [6-(1H-imidazol-1-yl)-7-nitro-2,3(1H,4H)-quinoxalinedione monohydrochloride], a decarboxymethylated form of zonampanel, was also used for comparing the substrate specificity. Zonampanel inhibited the uptake of prototypical organic anion substrates, [14C]para-aminohippurate in hOAT1 and [3H]estrone sulfate in hOAT3 and hOAT4, in a competitive manner. A time- and concentration-dependent increase in [14C]zonampanel uptake was observed in cells expressing hOAT1, hOAT3, and hOAT4. The Km values of zonampanel uptake by hOAT1, hOAT3, and hOAT4 were 1.4, 7.7, and 215 μM, resp. Considering the localization of each transporter, results suggest that zonampanel is taken up via hOAT1 and hOAT3 from the blood into proximal tubular cells and then effluxed into the lumen via hOAT4. Probenecid and cimetidine competitively inhibited [14C]zonampanel uptake by the hOATs (hOAT1, hOAT3, and hOAT4 for probenecid; hOAT3 for cimetidine). YM90K inhibited the uptake of the prototypical substrate via hOAT3 competitively, but the uptake via hOAT1 noncompetitively. These findings suggest that the prototypical organic anion substrates (para-aminohippurate and estrone sulfate), cimetidine, probenecid, and zonampanel share binding specificity in each hOAT, whereas YM90K does not in hOAT1, possibly due to it being the decarboxymethylated form.

IT 210245-80-0, Zonampanel
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(YM872; characterization of renal tubular transport of zonampanel, a novel AMPA receptor antagonist, by human organic anion transporters)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:633283 CAPLUS

DOCUMENT NUMBER: 141:167770

TITLE: Methods and compositions for treating inflammatory disorders of the airways

INVENTOR(S): Kurucz, Istvan; Solyom, Sandor; Perczel, Viola Csillik Nee

PATENT ASSIGNEE(S): Hung.

SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004152694	A1	20040805	US 2003-358061	20030204
WO 2004069195	A2	20040819	WO 2004-US3038	20040203
WO 2004069195	A3	20050113		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,

BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

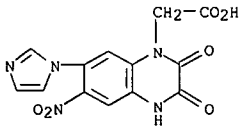
PRIORITY APPLN. INFO.: US 2003-358061 A 20030204

AB The invention provides compns. and methods for the treatment of inflammatory disorders of the airways by the administration of a therapeutically effective amount of a modulator according to the invention. More specifically, the invention relates to the treatment of airway inflammations including asthma or an asthma-related pathologies.

IT 210245-80-0, YM 872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for treating airway inflammatory disorders)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



L9 ANSWER 13 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:192846 CAPLUS

DOCUMENT NUMBER: 141:236253

TITLE: The glutamate AMPA receptor antagonist, YM872, attenuates regional cerebral edema and IgG immunoreactivity following experimental brain injury in rats

AUTHOR(S): Atsumi, T.; Hoshino, S.; Furukawa, T.; Kobayashi, S.; Asakura, T.; Takahashi, M.; Yamamoto, Y.; Teramoto, A.

CORPORATE SOURCE: Department of Emergency and Critical Care Medicine, Nippon Medical School, Tokyo, Japan

SOURCE: Brain Edema XII, Proceedings of the International Symposium, 12th, Hakone, Japan, Nov. 10-13, 2002 (2003), Meeting Date 2002, 305-307. Editor(s): Kuroiwa, T. Springer-Verlag Wien: Wien, Austria.
CODEN: 69FDSL; ISBN: 3-211-00919-1

DOCUMENT TYPE: Conference

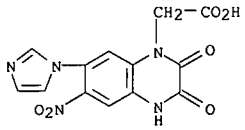
LANGUAGE: English

AB We previously reported the neuroprotective effects of the glutamate AMPA receptor antagonist YM872 on neurobehavioral motor function and cortical tissue loss (lesion volume) in a brain-injured rat model. Here we examined its effect on brain edema and the breakdown of the blood-brain barrier (BBB). Rats subjected to severe right lateral (parasagittal) fluid-percussion brain injury or sham injury received a 4-h i.v. infusion of YM872 (20 mg/kg/h, 20 mg/3 mL) or normal saline starting at 15 min post-injury. At 48 h we removed their brains and evaluated the cerebral regional edema by the wet weight/dry weight method. Another group of rats was transcardially fixed with 10% formalin at 2 wk after injury. Serial brain sections were immunostained for endogenous IgG and the extent and intensity of staining were evaluated. The administration of YMS72 resulted in a significant reduction in regional cerebral edema in the injured parietal cortex and a markedly reduced area of IgG immunoreactive in the injured cortex. Our results indicate that the post-traumatic administration of YM872 may be neuroprotective by reducing BBB breakdown and regional cerebral edema.

IT 210245-80-0, YM872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(YM872 reduced regional cerebral edema in injured parietal cortex and area of IgG immunoreactivity in injured cortex indicating that post-traumatic YM872 possibly neuroprotective by reducing BBB breakdown and regional cerebral edema in rat)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:20500 CAPLUS

DOCUMENT NUMBER: 140:53456

TITLE: Zonampanel (YM872) and its salts for treatment of brain hemorrhage

INVENTOR(S): Terai, Kazuhiro; Suzuki, Masanori; Sasamata, Masao

PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

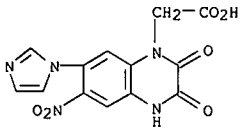
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004002488	A1	20040108	WO 2003-JP8128	20030626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2490688	A1	20040108	CA 2003-2490688	20030626
AU 2003243997	A1	20040119	AU 2003-243997	20030626
EP 1518556	A1	20050330	EP 2003-736270	20030626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005234063	A1	20051020	US 2004-519353	20041228
PRIORITY APPLN. INFO.:			JP 2002-188919 A	20020628
			WO 2003-JP8128 W	20030626

AB Zonampanel or its salt being an AMPA receptor antagonist, which exhibits amelioration effects for brain hemorrhage and neurol. symptoms associated with brain hemorrhage and hence is useful as a brain hemorrhage remedy.

IT 210245-80-0, Zonampanel 210245-80-0D, Zonampanel, salts
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zonampanel (YM872) and its salts for treatment of brain hemorrhage)

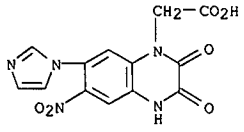
RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:796525 CAPLUS
DOCUMENT NUMBER: 139:297026
TITLE: Remedy for glioblastoma containing AMPA receptor antagonists
INVENTOR(S): Ishiuchi, Shogo
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

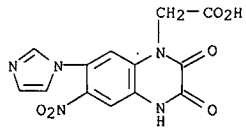
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003082332	A1	20031009	WO 2003-JP3867	20030327
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2479495	A1	20031009	CA 2003-2479495	20030327
AU 2003220825	A1	20031013	AU 2003-220825	20030327
EP 1491211	A1	20041229	EP 2003-715539	20030327
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1642572	A	20050720	CN 2003-807398	20030327
US 2005165009	A1	20050728	US 2003-509379	20030327
IN 2004KN01330	A	20060602	IN 2004-KN1330	20040910
PRIORITY APPLN. INFO.:			JP 2002-94313 A	20020329
			WO 2003-JP3867 W	20030327

AB It is intended to provide a novel remedy for glioblastoma. It is found out that a compound having an AMPA receptor antagonism is efficacious as a remedy for glioblastoma, in particular, highly malignant primary glioblastoma, thereby achieving the above object. The effect of 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline on glutamic acid-induced proliferation of human glioblastoma (CGNH-89) cells was examined Also, a freeze-dried composition containing [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxaline-1(2H)-yl]acetate monohydrate (zonampanel monohydrate) was formulated.

IT 210245-80-0, Zonampanel 466685-98-3, Zonampanel monohydrate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(remedy for glioblastoma containing AMPA receptor antagonists)

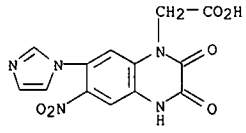
RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



RN 466685-98-3 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)



● H_2O

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:746343 CAPLUS
DOCUMENT NUMBER: 140:227
TITLE: Synthesis and AMPA receptor antagonistic activity of a novel class of quinoxalinecarboxylic acid with a

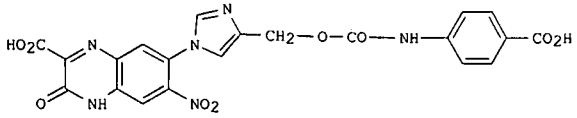
substituted phenyl group at the C-7 position

AUTHOR(S): Takano, Yasuo; Shiga, Futoshi; Asano, Jun; Ando, Naoki; Uchiki, Hideharu; Anraku, Tsuyosi

CORPORATE SOURCE: Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd., Nogi-machi, Simotsuga-gun, Tochigi, 329-0114, Japan

SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(20), 3521-3525
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:227

GI



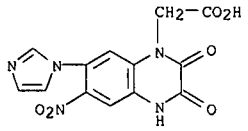
I

AB The synthesis and biol. properties of a novel class of 7-heterocycle-substituted quinoxalinecarboxylic acids, which bear a substituted Ph group through a urethane linkage at the C-7 position, are described. One of the synthesized compds., I, which has a 4-carboxyphenyl carbamoyloxymethyl imidazole group at the C-7 position and is water-soluble, was found to possess high potency in vitro and showed excellent neuroprotective efficacy in vivo.

IT 210245-80-0, YM-872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and AMPA receptor antagonistic activity of quinoxalinecarboxylates)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:434129 CAPLUS

DOCUMENT NUMBER: 139:962

TITLE: Composition for the treatment of ischemic stroke containing zonampanel and a tissue plasminogen activator

INVENTOR(S): Suzuki, Masanaori; Sasamata, Masao; Sumii, Toshihisa; Lo, Eng H.

PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

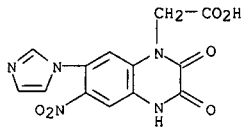
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1316313	A2	20030604	EP 2002-26909	20021203
EP 1316313	A3	20030709		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2003201238	A	20030718	JP 2002-349849	20021202
CA 2413491	A1	20030603	CA 2002-2413491	20021203
US 2003144295	A1	20030731	US 2002-307918	20021203
PRIORITY APPLN. INFO.:			US 2001-334556P P	20011203
			US 2002-361724P P	20020306

AB The present invention relates to a combination of zonampanel or its salt or hydrate together with a tissue plasminogen activator, administered together or one after another, for the therapy of ischemic stroke or for the improvement of neurol. symptom accompanied by cerebral infarction. The combination of the present invention showed better effect of reducing the infarct volume than administration of a single component. Therefore, the combination of the present invention is useful as a therapy for ischemic stroke.

IT 210245-80-0, Zonampanel 466685-98-3, Zonampanel monohydrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of zonampanel and tissue plasminogen activator for treatment of ischemic stroke)

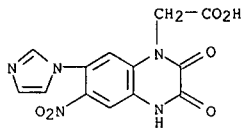
RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



RN 466685-98-3 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)

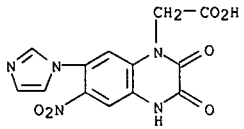


● H_2O

L9 ANSWER 18 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:295090 CAPLUS
DOCUMENT NUMBER: 139:191234
TITLE: Effect of AMPA receptor antagonist YM872 on cerebral hematoma size and neurological recovery in the intracerebral hemorrhage rat model
AUTHOR(S): Terai, Kazuhiro; Suzuki, Masanori; Sasamata, Masao; Yatsugi, Shin-Ichi; Yamaguchi, Tokio; Miyata, Keiji
CORPORATE SOURCE: Applied Pharmacology Research, Neuroscience Research, Yamanouchi Pharmaceutical Co., Ltd., Ibaraki, Tsukuba, 305-8585, Japan
SOURCE: European Journal of Pharmacology (2003), 467(1-3), 95-101
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB [2,3-Dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]-acetic acid monohydrate (YM872 or zonampanel), an AMPA receptor antagonist, is in clin. development for acute ischemic cerebral infarction. Stroke patients are prone to have subsequent intracerebral hemorrhages. To predict potential adverse effects, YM872 was tested in a rat model with collagenase-induced intracerebral hemorrhage. The morphol. determined hematoma vols. after 24 h were compared between animal groups i.v. infused with 3600 U/kg/h heparin for 30 min, or with 20 or 40 mg/kg/h of YM872, or placebo for 4 h. Heparin enlarged hematoma volume, but neither dose of YM872 affected hematoma size. In a sep. study, neurol. deficits were scored at various days after intracerebral hemorrhage induction in animals with i.v. infusion for 24 h of 10 or 20 mg/kg/h YM872, or saline. The YM872 groups scored significantly better than the saline group at 14 days. These data suggest that YM872 does not exacerbate intracerebral hemorrhage and might accelerate recovery.

IT 210245-80-0, YM872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of AMPA receptor antagonist YM872 on cerebral hematoma size and neurol. recovery in the intracerebral hemorrhage rat model)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)

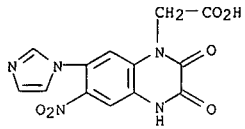


REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:196097 CAPLUS
DOCUMENT NUMBER: 139:317174
TITLE: DOPA cyclohexyl ester potently inhibits aglycemia-induced release of glutamate in rat striatal slices
AUTHOR(S): Hashimoto, Mizuki; Miyamae, Takeaki; Yamamoto, Isao; Goshima, Yoshio
CORPORATE SOURCE: Department of Molecular Pharmacology and Neurobiology, Yokohama City University School of Medicine, Yokohama, 236-0004, Japan
SOURCE: Neuroscience Research (Oxford, United Kingdom) (2003), 45(3), 335-344
CODEN: NERADN; ISSN: 0168-0102
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brain ischemic insult causes glutamate release and resultant neuronal cell death. We here show that L-3,4-dihydroxyphenylalanine (DOPA) is a pos. regulatory factor for glutamate release elicited by a mild brain insult using in vitro superfused rat striatal slices as a model system. Glucose deprivation for 18 min elicited release of glutamate, DOPA and dopamine (DA). Either tetrodotoxin (TTX) (1 μM) or α-methyl-p-tyrosine (α-MPT) (1 mM), a tyrosine hydroxylase inhibitor reduced markedly each of these releases. NSD-1015 (20 μM), an aromatic l-amino acid decarboxylase inhibitor restored the inhibition by α-MPT of glutamate and DOPA but not DA release. DOPA cyclohexyl ester (DOPA CHE) (0.3-1 μM), a competitive DOPA antagonist, concentration-dependently suppressed aglycemia-induced glutamate release, the effect which was mimicked neither by S-sulpiride nor SCH23390, a DA D1 or D2 receptor antagonist, resp. Zonisamide (1-1000 μM), an anticonvulsant or YM872 (1 μM), an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) a receptor antagonist produced no effect on aglycemia-induced glutamate release. DOPA CHE thus showed a relatively potent inhibitory action on aglycemia-induced glutamate release among several neuroprotective agents tested.

IT 210245-80-0, YM872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DOPA cyclohexyl ester potently inhibits aglycemia-induced release of glutamate in rat striatum)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:121866 CAPLUS
DOCUMENT NUMBER: 139:223419
TITLE: YM872: a selective, potent and highly water-soluble α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist
AUTHOR(S): Takahashi, Masayasu; Kohara, Atsuyuki; Shishikura, Jun-ichi; Kawasaki-Yatsugi, Sachiko; Ni, Jian Wei; Yatsugi, Shin-ichi; Sakamoto, Shuichi; Okada, Masamichi; Shimizu-Sasamata, Masao; Yamaguchi, Tokio
CORPORATE SOURCE: Neuroscience Research, Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, Japan
SOURCE: CNS Drug Reviews (2002), 8(4), 337-352
CODEN: CDREFB; ISSN: 1080-563X
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal; General Review

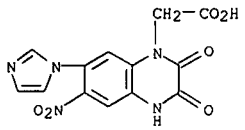
LANGUAGE: English

AB This review focuses on the in vitro and in vivo neuropharmacol. of YM872, a potential neuroprotective agent currently undergoing clin. trials in the United States (trial name: AMPA Receptor Antagonist Treatment in Ischemic Stroke - ARTIST). Its neuroprotective properties in rats and cats with induced focal cerebral ischemia are described. YM872, [2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydroquinoxalin-1-yl]-acetic acid monohydrate, is a selective, potent and highly water-soluble competitive α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist. YM872 has a potent inhibitory effect on [3H]AMPA binding with a Ki value of 0.096 μM. In contrast, YM872 has very low affinity for other ionotropic glutamate receptors. The solubility of YM872 is approx. 500 to 1000 times higher than that of the other competitive AMPA antagonists: YM90K, NBQX, or CNQX. The neuroprotective efficacy of YM872 was investigated in rats and cats subjected to permanent occlusion of the left middle cerebral artery. The animals were assessed either histol. or neurol. following ischemia. In rats with occluded middle cerebral artery (MCAO) YM872, by i.v. infusion, significantly reduced infarct volume measured at 24 h and 1 wk after ischemia. Significant neuroprotection was maintained even when drug administration was delayed for up to 2 h after ischemia. In addition, YM872 significantly improved neurol. deficit measured at 1 wk after ischemia. In cats with MCAO YM872, by i.v. infusion, dose-dependently reduced infarct volume at 6 h after ischemia. YM872 produced no behavioral abnormalities and was not nephrotoxic. The evidence for the neuroprotective efficacy of YM872 suggests its therapeutic potential in the treatment of acute stroke in humans.

IT 210245-80-0, YM872
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aminohydroxymethylisoxazolepropionic acid receptor antagonist YM872 in treatment of cerebral ischemia)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:931568 CAPLUS

DOCUMENT NUMBER: 139:774

TITLE: Neuroprotective effects of YM872 coadministered with t-PA in a rat embolic stroke model

AUTHOR(S): Suzuki, Masanori; Sasamata, Masao; Miyata, Keiji

CORPORATE SOURCE: Institute for Drug Discovery Research, Pharmacology Laboratories, Applied Pharmacology Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, Ibaraki, 305-8585, Japan

SOURCE: Brain Research (2003), 959(1), 169-172
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

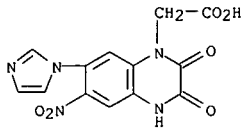
LANGUAGE: English

AB YM872, an AMPA receptor antagonist, was administered together with t-PA to investigate the effects of coadministration on neuroprotection in a rat embolic stroke model, when administered 2 h after embolism. T-PA or YM872 alone decreased infarct volume and improved the neurol. deficit score. Coadministration of YM872 and t-PA resulted in a further decrease in infarct volume and improvement of the neurol. score as compared with single administration of t-PA. These data demonstrate that coadministration of YM872 and t-PA produces more potent neuroprotective effects than when t-PA is administered alone.

IT 210245-80-0, YM872
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effects of AMPA receptor antagonist YM872 coadministered with thrombolytic t-PA in embolic stroke model)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:777693 CAPLUS

DOCUMENT NUMBER: 137:299911

TITLE: Neuroprotectant formulations

INVENTOR(S): Hesson, David P.; Frazer, Glenn D.; Ross, Douglas

PATENT ASSIGNEE(S): Neuron Therapeutics, Inc., USA

SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002078670	A1	20021010	WO 2002-US5885	20020228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002305940	A1	20021015	AU 2002-305940	20020228
EP 1370240	A1	20031217	EP 2002-733809	20020228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002193285	A1	20021219	US 2002-90441	20020304
PRIORITY APPLN. INFO.:			US 2001-331360P	P 20010302
			US 2001-798880	A 20010302
			WO 2002-US5885	W 20020228

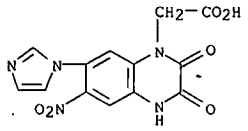
AB A method of treating an animal that has suffered damage to cerebrospinal tissue or that has an indication creating a risk of damage to

cerebrospinal tissue, comprises injecting a physiol. acceptable cerebrospinal perfusion fluid into a first catheter into the cerebrospinal pathway. The cerebrospinal perfusion fluid has a neuroprotecting effective amount of a neuroprotectant, withdrawing fluid at a second catheter into the cerebrospinal pathway to create a flow and flow pathway between the first and second catheters and c. maintaining the flow for a period of time adapted to perfuse an affected tissue.

IT 466685-98-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotectant formulations)

RN 466685-98-3 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrate (9CI) (CA INDEX NAME)



● H_2O

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

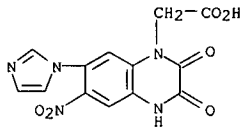
L9 ANSWER 23 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:219333 CAPLUS
DOCUMENT NUMBER: 135:174680
TITLE: The analgesic interaction between intrathecal clonidine and glutamate receptor antagonists on thermal and formalin-induced pain in rats
AUTHOR(S): Nishiyama, Tomoki; Gyermek, Laszlo; Lee, Chingmuh; Kawasaki-Yatsugi, Sachiko; Yamaguchi, Tokio; Hanaoka, Kazuo
CORPORATE SOURCE: Department of Anesthesiology Los Angeles Medical Center, Harbor-University of California, Torrance, CA, USA
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (2001), 92(3), 725-732
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clonidine, an α2 adrenergic receptor agonist, inhibits glutamate release from the spinal cord. The interaction of intrathecally administered clonidine and glutamate receptor antagonists on acute thermal or formalin-induced nociception was studied. Sprague-Dawley rats with lumbar intrathecal catheters were tested for their tail-withdrawal response by the tail flick test and paw flinches produced by formalin injection after intrathecal administration of saline, clonidine, AP-5 (2-amino-5-phosphonovaleric acid) (an NMDA receptor antagonist), or YM872 (an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist). The combinations of clonidine and the other two agents were also tested by isobolog. analyses. Motor disturbance and behavioral changes were observed as side effects. The ED50 values of clonidine decreased from 0.26 μg (tail flick), 0.12 μg (Phase 1) and 0.13 μg (Phase 2) to 0.036 μg, 0.006 μg, and 0.013 μg, resp., with AP-5, and to 0.039 μg, 0.057 μg, and 0.133 μg, resp., with YM872. Side effects were attenuated in both combinations. In conclusion, spinally administered clonidine and AP-5 or YM872 produced potent synergistic analgesia on acute thermal and formalin-induced nociception in rats, with decreased side effects.

IT 210245-80-0, YM 872
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(analgesic interaction between intrathecal clonidine and glutamate receptor antagonists)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:741905 CAPLUS
DOCUMENT NUMBER: 133:305610
TITLE: Treatment of neurological disorders with nitric oxide synthase inhibitors and excitatory amino receptor modulators
INVENTOR(S): O'Neill, Michael John
PATENT ASSIGNEE(S): Eli Lilly and Company Limited, UK
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061126	A2	20001019	WO 2000-GB1284	20000406
WO 2000061126	A3	20010823		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: GB 1999-8175 A 19990409

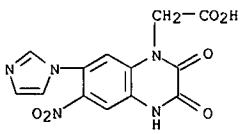
AB The present invention relates to a method of treating a neurol. disorder comprising administering to a patient an effective amount of a nitric oxide synthase inhibitor in combination with an effective amount of an excitatory amino receptor modulator. Combination of 2.5 mg/kg Mk-801, i.p., and 25 mg/kg ARL17477, i.p., had a synergistic degree of neuroprotection (78%) in cerebral ischemia induced in gerbils.

IT 210245-80-0, Ym872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(treatment of neurol. disorders with nitric oxide synthase inhibitors and excitatory amino receptor modulators)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



L9 ANSWER 25 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:715602 CAPLUS

DOCUMENT NUMBER: 133:281800

TITLE: Preparation of tetrahydroquinoxalines as AMPA receptor antagonists

INVENTOR(S): Hayashi, Yasumasa; Yoshida, Shinya; Ohsaki, Tomoaki

PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

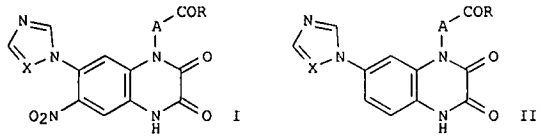
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000281676	A	20001010	JP 2000-13653	20000124
PRIORITY APPLN. INFO.:			JP 1999-15051 A	19990125

OTHER SOURCE(S): CASREACT 133:281800; MARPAT 133:281800

GI



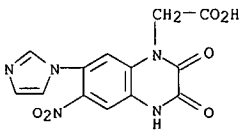
AB Title compds. I (A = lower alkylene; R = OH, lower alkoxy, lower alkyl-substituted amino; X= C, N), useful as pharmaceuticals for treatment of cerebrovascular diseases (no data), are prepared by nitration of quinoxalines II (A, R, X = same as I) with HNO3 in H2SO4 solution, dispersion of the reaction mixts. in H2O, hydrolysis of the resulting compds. in H2SO4, cooling, suspension, dissoln. in aqueous alkaline solution, neutralization with acids, and optionally, reaction with amines substituted by lower alkyl or lower alkyl. Et [2,3-dioxo-7-(1H-imidazol-1-yl)-1,2,3,4-tetrahydroquinoxalin-1-yl]acetate was reacted with HNO3 in the presence of H2SO4 at 0° for 2.5 h to give 64.0% Et [2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydroquinoxalin-1-yl]acetate sulfate, which was hydrolyzed in aqueous solution of H2SO4 at 101-102° for 3.5 h, treated with NaOH in H2O at ≤15°, and neutralized with HCl to give [2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydroquinoxalin-1-yl]acetic acid.

IT 210245-80-0P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrotetrahydroquinoxalines by nitration of tetrahydroquinoxalines, hydrolysis, treatment with alkalies, and neutralization)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



IT 299435-31-7P 299435-32-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nitrotetrahydroquinoxalines by nitration of tetrahydroquinoxalines, hydrolysis, treatment with alkalies, and neutralization)

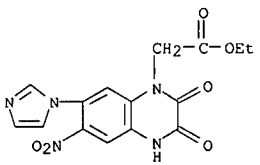
RN 299435-31-7 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, ethyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 179010-68-5

CMF C15 H13 N5 O6



CM 2

CRN 7664-93-9

CMF H2 O4 S

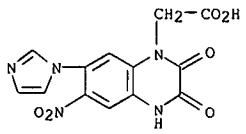
RN 299435-32-8 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-

dioxo-, sulfate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 210245-80-0
CMF C13 H9 N5 O6



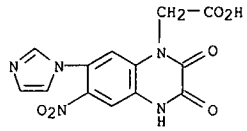
CM 2

CRN 7664-93-9
CMF H2 O4 S

L9 ANSWER 26 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:666600 CAPLUS
DOCUMENT NUMBER: 133:247292
TITLE: Amyotropic lateral sclerosis treatment with a combination of riluzole and an AMPA receptor antagonist
INVENTOR(S): Bohme, Andrees; Boireau, Alain; Canton, Thierry; Pratt, Jeremy; Stutzmann, Jean-Marie
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054772	A1	20000921	WO 2000-FR590	20000310
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2790670	A1	20000915	FR 1999-3100	19990312
EP 1161238	A1	20011212	EP 2000-910920	20000310
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539162	T	20021119	JP 2000-604848	20000310
PRIORITY APPLN. INFO.:			FR 1999-3100 A	19990312
			US 1999-129318P P	19990414
			WO 2000-FR590 W	20000310

OTHER SOURCE(S): MARPAT 133:247292
AB The invention discloses the prevention and/or treatment of amyotropic lateral sclerosis with a combination of riluzole and one or several AMPA receptor antagonists, as well as combinations of these compds. and pharmaceutical compns. containing them.
IT 210245-80-0, YM 872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(riluzole-AMPA receptor antagonist combination for treatment of amyotropic lateral sclerosis)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)

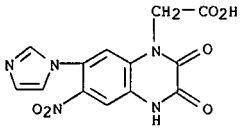


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

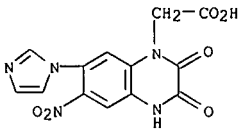
L9 ANSWER 27 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:452483 CAPLUS
DOCUMENT NUMBER: 133:68976
TITLE: Analgesics containing tetrahydroquinoxalinylacetic acid derivative
INVENTOR(S): Nishiyama, Tomoki
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000186041	A	20000704	JP 1999-360404	19991220
PRIORITY APPLN. INFO.:			US 1998-113097P P	19981221

AB 2,3-Dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinylacetic acid (I) or its salts are useful for prevention and treatment of acute or chronic pain. I and activators of benzodiazepine-GABA receptor complexes show synergistic analgesic activity to acute pain. Intraspinal injection of I showed analgesic activity with ED50 values of 0.24 μg and 0.21 μg in phase 1 and 2, resp., to formalin-induced pain in rats.
IT 210245-80-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesics containing tetrahydroquinoxalinylacetic acid derivative)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



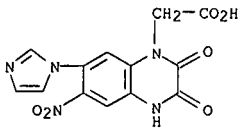
IT 210245-80-0D, mixts. containing 280104-99-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic analgesics containing tetrahydroquinoxalinylacetic acid derivative
and benzodiazepine-GABA receptor complex activators)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



RN 280104-99-6 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, mixt. with 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (9CI) (CA INDEX NAME)

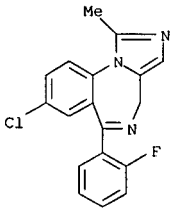
CM 1

CRN 210245-80-0
CMF C13 H9 N5 O6



CM 2

CRN 59467-70-8
CMF C18 H13 Cl F N3



L9 ANSWER 28 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:351162 CAPLUS
DOCUMENT NUMBER: 133:790
TITLE: New use of glutamate antagonists for the treatment of cancer
INVENTOR(S): Ikonomidou, Hrissanthi
PATENT ASSIGNEE(S): Germany
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

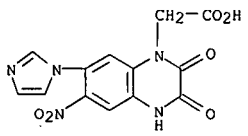
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1002535	A1	20000524	EP 1998-250380	19981028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9964750	A	20000515	AU 1999-64750	19991022
EP 1124553	A1	20010822	EP 1999-952622	19991022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528415	T	20020903	JP 2000-578005	19991022
EP 1586321	A1	20051019	EP 2005-12871	19991022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP 1649857	A2	20060426	EP 2005-12872	19991022
EP 1649857	A3	20070328		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 6797692	B1	20040928	US 2001-830354	20010425
US 2005054619	A1	20050310	US 2004-912159	20040806
US 2005054650	A1	20050310	US 2004-912175	20040806

PRIORITY APPLN. INFO.:

EP 1998-250380	A	19981028
EP 1999-952622	A3	19991022
WO 1999-EP8004	W	19991022
US 2001-830354	A3	20010425

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of cancer. Inhibitors of the interaction of glutamate with the AMPA, kainate, or NMDA receptor complexes are likely to be useful in treating cancer and can be formulated as pharmaceutical compns. They can be identified by appropriate screens.
IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment)
RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



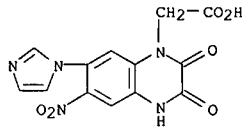
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 29 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:54684 CAPLUS
DOCUMENT NUMBER: 132:329238
TITLE: YM-872, Yamanouchi
AUTHOR(S): Danysz, Wojciech
CORPORATE SOURCE: Department of Pharmacological Research, Merz and Co., Frankfurt/Main, 60318, Germany
SOURCE: IDrugs (2000), 3(1), 84-89
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. Yamanouchi is developing YM-872, an AMPA receptor antagonist, as a potential treatment for cerebrovascular ischemia. It entered phase II trials in Europe in August 1998. It is undergoing phase I trials in Japan and was in phase II trials in the US as of August 1998. Yamanouchi hopes that YM-872 will be eligible for priority review and approval because of its new mechanism of action and the great medical need for such a drug. YM-872, an N-carboxymethyl derivative, displayed potent AMPA receptor affinity (Ki = 95 nM) and antikainate effect (IC50 = 0.8 μM) and was >500-fold more soluble than its parent compound YM-90K, allowing i.v. administration in a lower volume of infusion. Neuroprotective effects have been observed in a rat model of permanent focal ischemia. When given by infusion (20 mg/kg/h over 4 h), 1 h after exptl. ischemia, the drug was neuroprotective in the cortex (but not striatum) when measured 24 h after the ischemic insult. YM-872 has neuroprotective properties and ameliorates the deterioration of the hemodynamic penumbra by reducing the perfusion threshold for infarction after an episode of permanent focal ischemia. YM-872 reduced the atrophy of the substantia nigra in rats following middle cerebral artery occlusion. The therapeutic window of opportunity for YM-872 is 3 h in the above model.

IT 210245-80-0P, YM 872
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(pharmacol. of YM-872)

RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



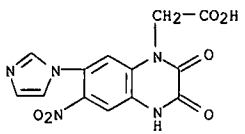
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 30 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:39234 CAPLUS
DOCUMENT NUMBER: 132:87574
TITLE: YM-872 Yamanouchi
AUTHOR(S): Danysz, Wojciech
CORPORATE SOURCE: Department of Pharmacological Research, Merz and Co., Frankfurt/Main, Germany
SOURCE: Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs (1999), 1(5), 677-682
CODEN: CCPRFX; ISSN: 1464-8482
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. Yamanouchi is developing YM-872, an AMPA receptor antagonist, as a potential treatment for cerebrovascular ischemia. It entered phase II trials in Europe in August 1998 [295049]. It is undergoing phase I trials in Japan [270568] and was in phase II trials in the US as of August 1998 [295049]. Yamanouchi hopes that YM-872 will be eligible for priority review and approval because of its new mechanism of action and the great medical need for such a drug [343645]. YM-872, an N-carboxymethyl derivative, displayed potent AMPA affinity (Ki = 95 nM), anti-kainate effect (IC50 = 0.8 μM) and was over 500-fold more soluble than its parent compound YM-90K, allowing iv administration in a lower volume of infusion [228599,294636]. Neuroprotective effects have been observed in a rat model of permanent focal ischemia. When given by infusion (20 mg/kg/h over 4 h), 1 h after exptl. ischemia, the drug was neuroprotective in the cortex (but not striatum) when measured 24 h after the ischemic insult. YM-872 has neuroprotective properties and ameliorates the deterioration of the hemodynamic penumbra by reducing the perfusion threshold for infarction after an episode of permanent focal ischemia [254092]. YM-872 significantly reduced the atrophy of the substantia nigra in rats following middle cerebral artery occlusion (MCAO) [307119]. The therapeutic window of opportunity for YM-872 is 3 h in the above model [324580]. In Feb. 1999, Lehman Brothers predicted the first major product launch to be in 2004, with sales peaking in 2012 [319225].

IT 210245-80-0, YM 872
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(YM-872 cerebrovascular anti-ischemic profile of)

RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)

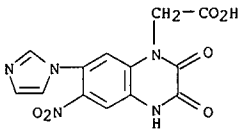


REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:15919 CAPLUS
DOCUMENT NUMBER: 132:288636
TITLE: The systemically administered competitive AMPA receptor antagonist, YM872, has analgesic effects on thermal or formalin-induced pain in rats
AUTHOR(S): Nishiyama, Tomoki; Gyermek, Laszlo; Lee, Chingmuh; Kawasaki-Yatsugi, Sachiko; Yamaguchi, Tokio
CORPORATE SOURCE: Department of Anesthesiology, Los Angeles Medical Center, Harbor-University of California, Torrance, CA, USA
SOURCE: Anesthesia & Analgesia (Baltimore) (1999), 89(6), 1534-1537
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new competitive α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, (2,3-dioxo-7-[1H-imidazol-1-yl]-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl) acetic acid (YM872), has analgesic effects on acute thermal- and formalin-induced nociception by intrathecal administration. The purpose of this study was to determine the analgesic effects of systemically administered YM872 in both acute thermal- and irritant-induced pain. Sprague-Dawley rats were tested for tail withdrawal response by the tail flick test and for paw flinches by formalin injection after i.p. administration of YM872. The tail flick latency increased dose-dependently with a 50% ED value of 156.3 μg. The number of flinches in both first and second phases of the formalin test decreased with increasing the dose of YM872. The 50% ED values were 1.0 μg in the first phase and 38.7 μg in the second phase. Transiently, i.p. administration of 1 and 10 mg YM872 induced motor disturbance and 10 mg induced loss of pinna reflex. Thus, i.p. administration of YM872 had analgesic effects on both acute thermal- and formalin-induced nociceptions in rats. Transient motor disturbance and loss of pinna reflex occurred only with large doses. Implications: I.p. administered YM872, a new α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, had analgesic effects on thermal- and formalin-induced pain in rats. Larger doses induced transient motor disturbance and loss of pinna reflex mediated in the brain.

IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic effects of systemically administered YM872 on thermal or formalin-induced pain)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)

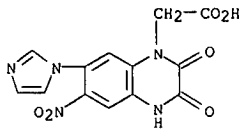


REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 32 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:7543 CAPLUS
DOCUMENT NUMBER: 132:202991
TITLE: Neuroprotective effects of an AMPA receptor antagonist YM872 in a rat transient middle cerebral artery occlusion model
AUTHOR(S): Kawasaki-Yatsugi, S.; Ichiki, C.; Yatsugi, S.-i.; Takahashi, M.; Shimizu-Sasamata, M.; Yamaguchi, T.; Minematsu, K.
CORPORATE SOURCE: Institute for Drug Discovery Research, Pharmacology Laboratories, Neuroscience Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, Ibaraki, Japan
SOURCE: Neuropharmacology (2000), 39(2), 211-217
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

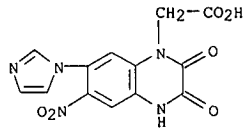
AB The neuroprotective effects of YM872 ([2,3-dioxo-7-(1H-imidazol-1-yl)6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]acetic acid monohydrate), a novel α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor antagonist with high water solubility, were examined in rats with transient middle cerebral artery (MCA) occlusion. The right MCA of male SD rats was occluded for 3 h using the intraluminal suture occlusion method. YM872 significantly reduced the infarct volume 24 h after occlusion, at dosages of 20 and 40 mg/kg/h (iv infusion) when given for 4 h immediately after occlusion. Furthermore, delayed administration of YM872 (20 mg/kg/h iv infusion for 4 h, starting 2 or 3 h after the occlusion) also reduced the infarct volume and the neurol. deficits measured at 24 h. Addnl., the therapeutic efficacy of YM872 persisted for at least seven days after MCA occlusion in animals treated with YM872 for 4 h starting 2 h after MCA occlusion. These data demonstrate that AMPA receptors contribute to the development of neuronal damage after reperfusion as well as during ischemia in the focal ischemia models and that the acute effect of the blockade of AMPA receptors persists over a long time period. YM872 shows promise as an effective treatment for patients suffering from acute stroke.

IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effects of an AMPA receptor antagonist YM872 in a rat transient middle cerebral artery occlusion model)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



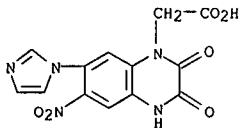
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 33 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:558670 CAPLUS
DOCUMENT NUMBER: 132:88054
TITLE: Analgesic interaction between intrathecal midazolam and glutamate receptor antagonists on thermal-induced pain in rats
AUTHOR(S): Nishiyama, Tomoki; Gyermek, Laszlo; Lee, Chingmuh; Kawasaki-Yatsugi, Sachiko; Yamaguchi, Tokio
CORPORATE SOURCE: Department of Anesthesiology, Harbor University of California, Los Angeles Medical Center, Los Angeles, CA, USA
SOURCE: Anesthesiology (1999), 91(2), 531-537
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study investigated the spinal analgesic interaction between midazolam, a benzodiazepine-GABAA receptor agonist, and 2 glutamate receptor antagonists with respect to acute thermal nociception. Rats were implanted with chronic lumbar intrathecal catheters and were tested for their tail-withdrawal response by the tail flick test after intrathecal administration of saline, midazolam (1-100 μg), AP-5 (1-30 μg), or YM872 (0.3-30 μg). AP-5 is an N-methyl-D-aspartate (NMDA) receptor antagonist and YM872 is an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist. The combination of midazolam and the other two agents was also tested by isobolog. analyses. Side effects (motor disturbance and behavioral changes) were studied. Dose-dependent increases in the tail flick latency were observed with midazolam, AP-5, and YM872 singly, with ED50 values of 1.57, 5.54, and 1.0 μg, resp. A potent synergy in analgesia, with decreased behavioral changes and motor disturbance, was obtained when combining midazolam with AP-5 or YM872. Thus, spinally administered midazolam and an NMDA or an AMPA receptor antagonist produced potent synergistic analgesia to acute thermal nociception in rats. Side effects, shown by behavioral changes and motor disturbance, decreased with the combination of the agents.
IT 210245-80-0, YM 872
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(analgesic interaction between intrathecal midazolam and glutamate receptor antagonists)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



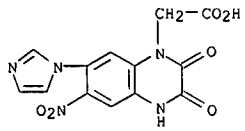
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 34 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:442943 CAPLUS
DOCUMENT NUMBER: 131:281358
TITLE: The spinal antinociceptive effects of a novel competitive AMPA receptor antagonist, YM872, on thermal or formalin-induced pain in rats
AUTHOR(S): Nishiyama, Tomoki; Gyermek, Laszlo; Lee, Chingmuh; Kawasaki-Yatsugi, Sachiko; Yamaguchi, Tokio
CORPORATE SOURCE: Department of Anesthesiology, Los Angeles Medical Center, Harbor-University of California, Torrance, CA, USA
SOURCE: Anesthesia & Analgesia (Baltimore) (1999), 89(1), 143-147
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonists have spinally mediated analgesic effects on acute nociception; however, their current formulations are not water-soluble and have toxic side effects. A new competitive AMPA antagonist, YM872 (2,3-dioxo-7-[1H-imidazol-1-yl]-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinylacetic acid) is water-soluble and may have fewer side effects. This study investigated the analgesic effects of YM872 on both acute thermal and irritant-induced pain. Sprague-Dawley rats were implanted with chronic lumbar intrathecal catheters and were tested for their tail withdrawal response to thermal pain and for their paw flinch response to formalin injection after the intrathecal administration of YM872. The tail flick latency increased dose-dependently, with an ED50 of 1.0 μg. The number of flinches in both Phase 1 and Phase 2 of the formalin test decreased with increasing doses of YM872. ED50 values were 0.24 μg in Phase 1 and 0.21 μg in Phase 2. YM872 at high doses (10 and 30 μg) induced motor disturbance and flaccidity. Thus, in rats, the intrathecal administration of YM872 had analgesic effects on both acute thermal and formalin-induced nociceptions. Transient motor disturbance and flaccidity occurred only with large doses. YM872 may have potential in the clin. management of both acute and chronic pain.
IT 210245-80-0, YM 872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(spinal antinociceptive effects of AMPA receptor antagonist YM872 on thermal or formalin-induced pain)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



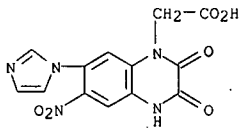
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 35 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:2173 CAPLUS
DOCUMENT NUMBER: 130:218090
TITLE: Effects of YM872 on atrophy of substantia nigra reticulata after focal ischemia in rats
AUTHOR(S): Ni, Jian Wei; Takahashi, Masayasu; Yatsugi, Shin-ichi; Shimizu-Sasamata, Masao; Yamaguchi, Tokio
CORPORATE SOURCE: Neuroscience Research, Pharmacology Laboratories, Institute for Drug Discovery Research, Ibaraki, 305-8585, Japan
SOURCE: NeuroReport (1998), 9(16), 3719-3724
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Middle cerebral artery (MCA) occlusion causes atrophy in the ipsilateral substantia nigra reticulata (SNR). The effects of glutamate AMPA receptor antagonism on SNR atrophy, which is supposed to inhibit excitatory inputs from the subthalamic nucleus to the SNR, was investigated in rats with permanent MCA occlusions. Histol. examination revealed marked atrophy two weeks after MCA occlusion in the saline-treated control group. However, constant i.v. infusion of YM872, a selective AMPA receptor antagonist, for 2 wk significantly reduced SNR atrophy; neurol. deficits also decreased. These results suggest that the AMPA receptor may be involved in the pathogenesis of SNR atrophy during the subacute phase of focal cerebral ischemia.
IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of YM872 on atrophy of substantia nigra reticulata after focal ischemia in rats in relation to role of AMPA receptors)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 36 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:743856 CAPLUS
DOCUMENT NUMBER: 130:105240
TITLE: Neuroprotective efficacy of YM872, an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, after permanent middle cerebral artery occlusion in rats
AUTHOR(S): Takahashi, Masayasu; Ni, Jian Wei; Kawasaki-Yatsugi, Sachiko; Toya, Takashi; Ichiki, Chikako; Yatsugi, Shin-Ichi; Koshiya, Kazuo; Shimizu-Sasamata, Masao; Yamaguchi, Tokio
CORPORATE SOURCE: Neuroscience Research, Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305-8585, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 287(2), 559-566
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Lippencott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The neuroprotective efficacy of YM872, a novel, highly water-soluble α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, was investigated in rats subjected to permanent occlusion of the left middle cerebral artery. The rats were assessed either histol. or neurol. 24 h or 1 wk after ischemia. YM872 was i.v. infused for either 4 or 24 h at dose rates of 0 to 20 mg/kg/h starting 5 min after ischemia to examine the effect of prolonged treatment. YM872 was then infused at 20 mg/kg/h beginning 0 to 4 h after ischemia to determine the efficacy time window. Addnl., a 20 mg/kg/h dose rate of YM872 was infused for 4 h in single day- or 5-day repetitive-administrations to evaluate long-term benefits of the drug. YM872 significantly reduced infarct volume in both 4- and 24-h treatment groups measured 24 h after ischemia. No difference was observed in the degree of protection between length of infusion. Significant neuroprotection was maintained even when drug administration was delayed up to 2 h after ischemia. A single YM872-administration significantly improved neurol. deficit and reduced infarct volume (30%, P < .01) measured 1 wk after ischemia. YM872 treatment did not induce such adverse effects as physiol. changes, serious behavioral abnormalities or nephrotoxicity. These data suggest that the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor plays a crucial role in the progression of neuronal damage in the early phase of ischemia and that YM872 may be useful in treating acute ischemic stroke.
IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effect of AMPA receptor antagonist YM872)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 37 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:692565 CAPLUS
DOCUMENT NUMBER: 130:90401
TITLE: YM872, a highly water-soluble AMPA receptor

antagonist, preserves the hemodynamic penumbra and reduces brain injury after permanent focal ischemia in rats

AUTHOR(S): Shimizu-Sasamata, Masao; Kano, Tsuneo; Rogowska, Jadwiga; Wolf, Gerald L.; Moskowitz, Michael A.; Lo, Eng H.

CORPORATE SOURCE: Departments of Neurosurgery and Neurology, Stroke and Neurovascular Regulation Laboratory, Harvard Medical School, Massachusetts General Hospital, Charlestown, MA, 02129, USA

SOURCE: Stroke (1998), 29(10), 2141-2147
CODEN: SJCCA7; ISSN: 0039-2499

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

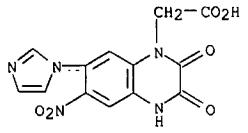
LANGUAGE: English

AB We recently described an image anal. technique based on the temporal correlation mapping (TCM) of injected contrast agents that can be used to distinguish the hemodynamic core and hemodynamic penumbra after focal ischemia. In this study we used this technique for the first time to investigate the effects of the water-soluble AMPA receptor antagonist YM872 in permanent focal ischemia. Fischer 344 rats were subjected to permanent occlusion of the middle cerebral artery. Approx. 30 min after ischemia, functional CT images were collected with the use of a dynamic scanning protocol with bolus injections of nonionic contrast agent iohexol (1 mL/kg). TCM anal. defined the distributions of hemodynamic core and hemodynamic penumbra. Cerebral perfusion indexes were calculated on the basis of the area under the first-pass transit curves. One hour after ischemia, animals were randomly treated with YM872 (n=8, 20 mg/kg per h over 4 h) or normal saline (n=10). Twenty-four hours later, neurol. deficits were evaluated, and conventional CT and triphenyltetrazolium chloride staining were used to define vols. of ischemic damage. At 24 h after ischemia, hypodense lesions were visible on conventional CT scans that were highly correlated with triphenyltetrazolium chloride lesion vols. YM872 improved neurol. deficits and reduced vols. of ischemic damage in cortex (90±14 vs. 170±16 mm3 in controls) but not striatum (57±14 vs. 79±6 mm3 in controls). Comparison of early TCM images with conventional CT scans of ischemic injury showed that the hemodynamic core was always damaged in all rats. In controls, 54% of the tissue within the hemodynamic penumbra evolved into ischemic damage compared with 24% in YM872-treated rats. Furthermore, the perfusion index corresponding to the ischemic damage threshold was significantly reduced by YM872 (28±2% vs. 37±2% in controls). These results indicate that YM872 is a neuroprotective compound that ameliorates the deterioration of the hemodynamic penumbra after focal ischemia.

IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(YM872, water-soluble AMPA receptor antagonist, preserves hemodynamic penumbra and reduces brain injury after permanent focal ischemia in rats)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:691232 CAPLUS

DOCUMENT NUMBER: 130:133986

TITLE: Neuroprotective effect of the novel glutamate AMPA receptor antagonist YM872 assessed with in vivo MR imaging of rat MCA occlusion

AUTHOR(S): Haberg, Asta; Takahashi, Masayasu; Yamaguchi, Tokio; Hjelstuen, Mari; Haraldseth, Olav

CORPORATE SOURCE: RIT, MR-Center, University Hospital, Trondheim, N-7006, Norway

SOURCE: Brain Research (1998), 811(1,2), 63-70
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

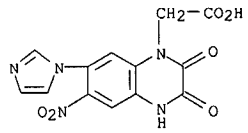
LANGUAGE: English

AB The neuroprotective effect of post-ischemic treatment with the novel, highly water-soluble, glutamate AMPA receptor antagonist YM872 was evaluated by using MR imaging and histopathol. of rats subjected to permanent MCA occlusion. Two treatment groups with continuous i.v. infusion of 20 mg kg-1 h-1 YM872 during either the first 4 h or first 24 h after MCA occlusion, called 4 h YM872 treatment group (n=9) and 24 h YM872 treatment group (n=8) resp., were compared to a control group (n=8). The main end-point was T2 weighted MR imaging and histopathol. 24 h after MCA occlusion. Also the time evolution of the ischemic tissue damage was studied by diffusion weighted MR imaging 4 and 24 h after MCA occlusion. The volume of ischemic tissue damage as assessed by diffusion weighted MR imaging 4 h after MCA occlusion was significantly smaller in both YM872 treatment groups (99±52 mm3 and 102±44 mm3 compared to 186±72 mm3 in the control group, ±S.D. and p=0.008). The infarct volume as assessed by T2 weighted MR imaging 24 h after MCA occlusion was significantly smaller only in the 24 h YM872 treatment group (262±57 mm3 compared to 366±49 mm3 in the control group, ±S.D. and p=0.01) while the infarct volume in the 4 h YM872 treatment group (357±88 mm3) was similar to the control group. YM872 treatment significantly reduced the infarct volume 24 h after MCA occlusion when the drug was administered as continuous infusion during the 24-h observation period.

IT 210245-80-0, YM872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effect of AMPA receptor antagonist YM872 assessed with in vivo MR imaging of rat MCA occlusion)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 39 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:515232 CAPLUS

DOCUMENT NUMBER: 129:225643

TITLE: In-vitro characterization of YM872, a selective, potent and highly water-soluble α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist

AUTHOR(S): Kohara, Atsuyuki; Okada, Masamichi; Tsutsumi, Rie; Ohno, Kazushige; Takahashi, Masayasu; Shimizu-Sasamata, Masao; Shishikura, Jun-Ichi; Inami, Hiroshi; Sakamoto, Shuichi; Yamaguchi, Tokio

CORPORATE SOURCE: Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd, Tsukuba City, 305, Japan

SOURCE: Journal of Pharmacy and Pharmacology (1998), 50(7), 795-801
CODEN: JPPMAB; ISSN: 0022-3573

PUBLISHER: Royal Pharmaceutical Society of Great Britain

DOCUMENT TYPE: Journal

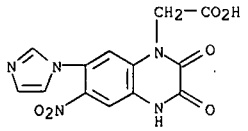
LANGUAGE: English

AB The in-vitro pharmacol. properties of (2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl)-acetic acid monohydrate, YM872, a novel and highly water-soluble α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-receptor antagonist were investigated. YM872 is highly water soluble (83 mg mL-1 in Britton-Robinson buffer) compared with 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX), 6-(1H-imidazol-1-yl)-7-nitro-2,3(1H,4H)-quinoxalinedione hydrochloride (YM90K) or 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). YM872 potently inhibits [3H]AMPA binding with a Ki (apparent equilibrium dissociation constant) value of 0.096 μM. However, YM872 had very low affinity for other ionotropic glutamate receptors, as measured by competition with [3H]kainate (high-affinity kainate binding site, concentration resulting in half the maximum inhibition (IC50) = 4.6 μM), [3H]glutamate (N-methyl-D-aspartate (NMDA) receptor glutamate binding site, IC50>100 μM) and [3H]glycine (NMDA receptor glycine-binding site, IC50>100 μM). YM872 competitively antagonized kainate-induced currents in Xenopus laevis oocytes which express rat AMPA receptors, with a pA2 value of 6.97. In rat hippocampal primary cultures, YM872 blocked a 20-μM AMPA-induced increase of intracellular Ca2+ concentration with an IC50 value of 0.82 μM, and blocked 300-μM kainate-induced neurotoxicity with an IC50 value of 1.02 μM. These results show that YM872 is a potent and highly water-soluble AMPA antagonist with great potential for treatment of neurodegenerative disorders such as stroke.

IT 210245-80-0, YM 872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(YM 872; in-vitro characterization of YM872 as selective and potent and highly water-soluble AMPA receptor antagonist with neuroprotectant activity)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 40 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:409554 CAPLUS

DOCUMENT NUMBER: 129:156820

TITLE: Neuroprotective effects of a novel AMPA receptor antagonist, YM872

AUTHOR(S): Small, Daniel L.; Murray, Christine L.; Monette, Robert; Kawasaki-Yatsugi, Sachiko; Morley, Paul

CORPORATE SOURCE: Cellular Neurobiology Group, Institute for Biological Sciences, National Research Council of Canada, Ottawa, ON, K1A OR6, Can.

SOURCE: NeuroReport (1998), 9(7), 1287-1290
CODEN: NERPEZ; ISSN: 0959-4965

PUBLISHER: Rapid Science Publishers

DOCUMENT TYPE: Journal

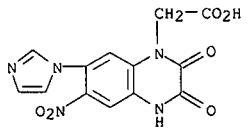
LANGUAGE: English

AB Quinoxalinediones such as NBQX are neuroprotective in most models of cerebral ischemia but their poor solubility results in nephrotoxicity limiting their clin. utility. The authors have investigated the neuroprotective effects of a water soluble AMPA receptor antagonist, YM872, using two in vitro models. The viability of cortical cultures exposed to 400 μM AMPA for 15 min (16.4 ± 2.6%; n = 10) was significantly ($p < 0.05$) increased (84.7 ± 4.6%; n = 6) with YM872 (10 μM) in a concentration-dependent manner. Evoked post-synaptic response amplitudes in oxygen-glucose deprived hippocampal slices treated with 10 μM YM872 (3.5 ± 0.3 mV; n = 27) were significantly different from untreated deprived slices (0.3 ± 0.1 mV; n = 31, $p < 0.05$) and the CA1 neurons appeared viable using a confocal live/dead fluorescence assay with confocal microscopy. The neuroprotection seen with YM872 in vitro warrants further investigation in vivo.

IT 210245-80-0, YM 872
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effects of a novel AMPA receptor antagonist, YM872)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 41 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:343162 CAPLUS

DOCUMENT NUMBER: 129:117773

TITLE: A novel AMPA receptor antagonist, YM872, reduces infarct size after middle cerebral artery occlusion in rats

AUTHOR(S): Kawasaki-Yatsugi, Sachiko; Yatsugi, Shin-ichi; Takahashi, Masayasu; Toya, Takashi; Ichiki, Chikako; Shimizu-Sasamata, Masao; Yamaguchi, Tokio; Minematsu, Kazuo

CORPORATE SOURCE: Pharmacological Laboratory, Neuroscience Research, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical, Tsukuba, Japan

SOURCE: Brain Research (1998), 793(1,2), 39-46
CODEN: BRREAP; ISSN: 0006-8993

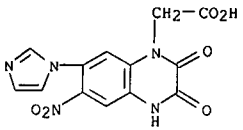
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuroprotective effect of YM-872 ([2.3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]acetic acid monohydrate), a novel α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonist with improved water solubility, was examined in the rat focal cerebral ischemia model. Rats were subjected to permanent middle cerebral artery (MCA) occlusion using the intraluminal suture occlusion method for 24 h. YM-872 was infused i.v. for 4 h (20 and 40 mg/kg/h) or 24 h (10 and 20 mg/kg/h), starting 5 min after the MCA occlusion, to investigate the effect of prolonged YM-872 treatment on infarction volume In the 4 h infusion study, YM-872 reduced the cortical infarction volume by 48% at a dose of 40 mg/kg/h. YM-872 did not reduce the infarction size at 20 mg/kg/h for 4 h. In the 24-h infusion study, YM-872 markedly reduced the cortical infarction volume by 62% even at 20 mg/kg/h. Thus, the neuroprotective effects of YM-872 are enhanced by extending the duration of treatment. YM-872 is applicable to investigate the role of AMPA receptors in ischemic models without concern about nephrotoxicity and could be useful in the treatment of human stroke.

IT 210245-80-0, YM 872
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(YM-872 antagonist of AMPA receptors reduces infarction size after middle cerebral artery occlusion in rats)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 42 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:451993 CAPLUS
DOCUMENT NUMBER: 125:114689
TITLE: Preparation of 1,2,3,4-tetrahydroquinoxaline-2,3-dione derivatives as NMDA-glycine receptor and/or AMPA receptor antagonists and kainate neurocytotoxicity inhibitors
INVENTOR(S): Shishikura, Jun-ichi; Inami, Hiroshi; Sakamoto, Shuichi; Tsukamoto, Shin-ichi; Sasamata, Masao; Okada, Masamichi; Fujii, Mitsuo
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9610023	A1	19960404	WO 1995-JP1922	19950925
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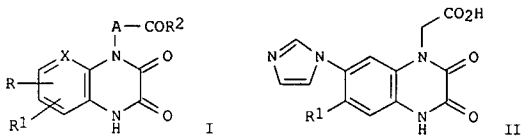
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2199468	A1	19960404	CA 1995-2199468	19950925
CA 2199468	C	20060606		
AU 9535337	A	19960419	AU 1995-35337	19950925
AU 684392	B2	19971211		
EP 784054	A1	19970716	EP 1995-932217	19950925
EP 784054	B1	20011128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CN 1168670	A	19971224	CN 1995-195237	19950925
CN 1067387	B	20010620		
HU 77442	A2	19980428	HU 1997-2043	19950925
HU 223945	B1	20050329		
JP 2865878	B2	19990308	JP 1996-511593	19950925
RU 2149873	C1	20000527	RU 1997-104870	19950925
PL 181532	B1	20010831	PL 1995-320059	19950925
AT 209644	T	20011215	AT 1995-932217	19950925
PT 784054	T	20020531	PT 1995-932217	19950925
ES 2168383	T3	20020616	ES 1995-932217	19950925
US 6096743	A	20000801	US 1997-809087	19970305
PRIORITY APPLN. INFO.:			JP 1994-231908	A 19940927
			JP 1995-59482	A 19950317
			WO 1995-JP1922	W 19950925

OTHER SOURCE(S): MARPAT 125:114689
GI

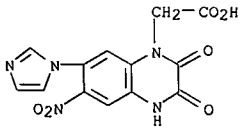


AB The title compds. [I; X = N or CH; R = imidazolyl or di(lower alkyl)amino; R1 = (1) halo, nitro, cyano, carboxy, amino, mono- or di(lower alkyl)amino, lower alkanoyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, or carbamoyl, (2) lower alkyl or lower alkoxy which may be substituted by halo, carboxy or aryl, or (3) phenyloxy which may be substituted by lower alkoxycarbonyl or carboxy; R2 = hydroxy, lower alkoxy, amino, or mono- or di(lower alkyl)amino; A = optionally substituted alkylene or O-B (B being lower alkylene); provided the case wherein R represents imidazolyl, R1 represents cyano, A represents ethylene and R2 represents hydroxy is excepted], which have high affinity for AMPA receptor of non-NMDA receptor and high solubility and suppress audiogenic convulsion, are prepared A glutamate receptor antagonist, NMDA-glycine receptor and/or AMPA receptor antagonist, a kainate neurocytotoxicity inhibitor, a psychotropic, and a remedy for ischemia contains I. Thus, 2,4-difluoronitrobenzene was added to a mixture of Et glycinate hydrochloride, Et3N, and THF and refluxed for 3 h to give 71.5% Et N-(2-nitro-5-fluorophenyl)glycinate, which was hydrogenated in the presence of 10% Pd-C in MeOH and stirred with Et chloroglyoxylate and Et3N in CHCl3 at room temperature for 1 h to give 80% Et 2-(7-fluoro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-1-yl)acetate. The latter compound was nitrated by fuming HNO3 in concentrated H2SO4 to give 96% Et 2-(7-fluoro-6-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-1-yl)acetate, which was heated with imidazole in DMF at 120° for 6 h followed by saponification with 1 N aqueous NaOH and acidification with 1 N aqueous HCl to pH .apprx.3.5 to give the title

compound (II; R1 = NO2). The latter compound and II (R1 = PhCH2O) in vitro inhibited the binding of [3H]-AMPA to rat cerebral membrane sample with Ki value of 0.093 and 0.07 μM, resp. A vial formulation containing II (R1 = NO2) was described.

IT 179010-47-0P 179010-75-4P 179010-76-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tetrahydroquinoxalinedione derivs. as NMDA-glycine receptor and/or AMPA receptor antagonists, kainate neurocytotoxicity inhibitors, psychotropics, and ischemia remedy)

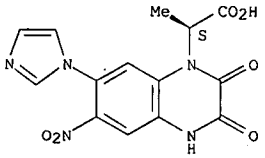
RN 179010-47-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 179010-75-4 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-α-methyl-6-nitro-2,3-dioxo-, monohydrochloride, (S)- (9CI) (CA INDEX NAME)

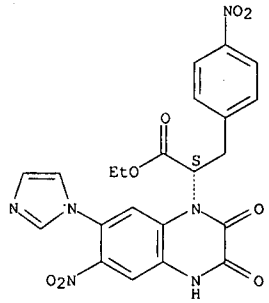
Absolute stereochemistry.



● HCl

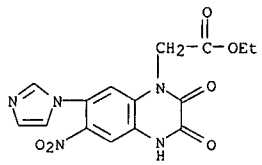
RN 179010-76-5 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-α-[(4-nitrophenyl)methyl]-2,3-dioxo-, ethyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 179010-68-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tetrahydroquinoxalinedione derivs. as NMDA-glycine receptor and/or AMPA receptor antagonists, kainate neurocytotoxicity inhibitors, psychotropics, and ischemia remedy)

RN 179010-68-5 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



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